THERAPEUTIC AGENTS II

Field of invention

The present invention relates to certain *N*-cycloalkyl, aryl or heteroaryl- *N'*-quinazolin-2-yl cycloalkyldiamines of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, and to pharmaceutical compositions containing them.

Background of the invention

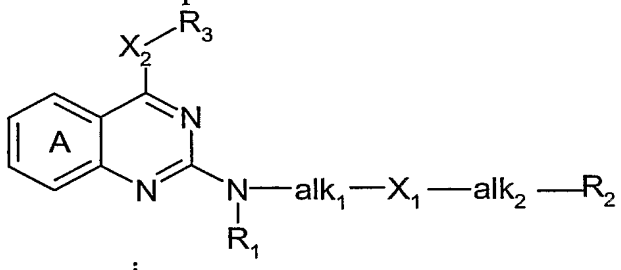
Melanin concentrating hormone (MCH) is a cyclic peptide that was first isolated from fish over 15 years ago. In mammals, MCH gene expression is localised to the ventral aspect of the zona inserta and the lateral hypothalamic area (Breton et al., Molecular and Cellular Neurosciences, vol. 4, 271-284 (1993)). The latter region of the brain is associated with the control of behaviours such as eating and drinking, with arousal and with motor activity (Baker, B., Trends Endocrinol. Metab. 5: 120-126(1994), vol. 5, No. 3, 120-126 (1994)). Although the biological activity in mammals has not been fully defined, recent work has indicated that MCH promotes eating and weight gain (US 5,849,708). Thus, MCH and its agonists have been proposed as treatments for anorexia nervosa and weight loss due to AIDS, renal disease, or chemotherapy. Similarly, antagonists of MCH can be used as a treatment for obesity and other disorders characterised by compulsive eating and excessive body weight. MCH projections are found throughout the brain, including the spinal cord, an area important in processing nociception, indicates that agents acting through MCH1r, such as compounds of formula I, will be useful in treating pain.

Two receptors for MCH (MCH1r (Shimomura et al. Biochem Biophys Res Commun 1999 Aug 11;261(3):622-6) & MCH2r (Hilol et al. J Biol Chem. 2001 Jun 8;276(23):20125-9)) have been identified in humans, while only one (MCH1r) is present in rodent species (Tan et al. Genomics. 2002 Jun;79(6):785-92). In mice lacking MCH1r, there is no increased feeding response to MCH, and a lean phenotype is seen, suggesting that this receptor is responsible for mediating the feeding effect of MCH (Marsh et al. Proc Natl Acad Sci U S A. 2002 Mar 5;99(5):3240-5). In addition, MCH receptor antagonists have been demonstrated to block the feeding effects of MCH (Takekawa et al. Eur J Pharmacol. 2002 Mar 8;438(3):129-35), and to reduce body weight & adiposity in diet-induced obese rats

(Borowsky et al. Nat Med. 2002 Aug;8(8):825-30). The conservation of distribution and sequence of MCH1r suggest a similar role for this receptor in man and rodent species. Hence, MCH receptor antagonists have been proposed as a treatment for obesity and other disorders characterised by excessive eating and body weight.

US 5,874,438 discloses 2,2'-bridged bis-2,4-diaminoquinazolines are apamine-sensitive potassium channel blockers which are useful in the treatment of dementia, depression, myotonic dystrophy or asthma. N2, N2'-(1,3-cyclohexanediylbis(methylene))bis(N4,N4'-diethyl-2,4-quinazolinediamine is exemplified.

Claim 1 of WO97/20823 was considered to be of very broad scope and vague and therefore unsearchable by the European Patent Office. The search was limited to the Examples. The document discloses quinazolines of formula i



i

in which X_2 is –O-, $S(O)_n$ or a group of the formula –$N(R_4)$, alk_1 is a bond or lower alkylene, X_1 is *inter alia* C_3-C_8 cycloalkylene or alk_2 is a bond or lower alkylene, R_1 is *inter alia* H or lower alkyl, R_2 is *inter alia* substituted amino where the substitution is *inter alia* by (carbocyclic or heterocyclic) aryl or (carbocyclic or heterocyclic) aryl-loweralkyl, R_3 and R_4 are *inter alia* H or lower alkyl, and A is a wide range of substituents. The compounds are claimed to be NPY 5 antagonists and therefore useful in the treatment of *inter alia* obesity and diabetes. Most of the examples are naphthalenesulphonamides, amides or have a 4-anilino substituent in the quinazolyl ring . However, none of the compounds exemplified in this application fall within the scope of the present application.

WO 03/028641 discloses that compounds of formula ii

Q-L-Y-R_1

ii

in which *inter alia* Q is 4-substitutedamino-2-quinazolyl which is unsubstituted in the 5, 6, 7 or 8 positions, L is *inter alia* 1,4-diaminocyclohexyl wherein there is an optionally an

alklylene group between each amine and the cyclohexyl ring, Y is a bond, methylene, carbonyl, or sulphonyl, and R_1 is *inter alia* heteroaryl are MCH receptor antagonists. Co-pending application WO2004/087680 discloses compounds of formula iii

$$Q\text{-}L\text{-}Y\text{-}R_1$$

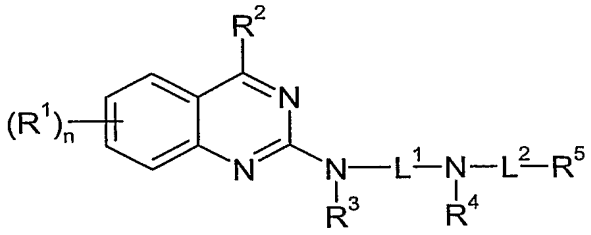
iii

in which Q is substituted quinazolyl, L is 1,4-diaminocyclohexyl or 1,3-diamino-cyclopentyl wherein there is an optionally an alklylene group between each amine and the cycloalkyl ring, Y is C(O)NR, C(S)NR, C(O)O, a bond or CH_2 and R_1 is inter alia phenyl or heterocyclyl are MCH receptor antagonists.

There is an umet need for MCH receptor antagonists that are more potent, more selective, more bioavailable and less toxic than known compounds in this field. The present invention provides additional compounds that are MCH1r antagonists which are useful in treating obesity and related disorders, psychiatric disorders, neurological disorders and pain.

Description of the invention

The present invention relates to a compound of formula I



I

wherein

R^1 represents a) a C_{1-4} alkoxy group optionally substituted by one or more fluoro, b) a C_{1-4} alkyl group optionally substituted by one or more fluoro, c) halo, d) cyano, e) a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O atom f) a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring, or g) a group $-OSO_2C_{1-4}$alkyl optionally substituted by one or more fluoro;

n represents 0, 1, 2 or 3 ;

R^2 represents H or cyano or a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4} alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O, a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

R^3 represents H or a C_{1-4} alkyl group;

L^1 represents a $(CH_2)_pC_{3-10}$ cycloalkyl group in which p is 0 or1 and in which the cycloalkyl group may be monocyclic or bicyclic and optionally may be bridged provided that the two nitrogens bearing R^3 and R^4, respectively, are not linked to the same carbon atom, and wherein one of the carbons may be replaced by O; with the proviso that L^1 does not represent 1,3-cyclopentyl or 1,4-cyclohexyl;

R^4 represents H or a C_{1-4} alkyl group optionally substituted by one or more of the following: fluoro or C_{1-4} alkoxy optionally substituted by one or more fluoro;

L^2 represents an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: fluoro or C_{1-4} alkyl;

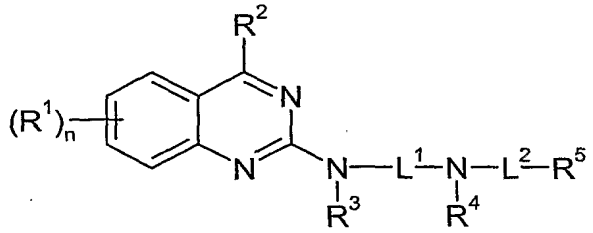
L^2 may also represent a 5-6 membered carbocyclic 5-6 membered ring fused to R^5;

R^5 represents phenyl or naphthyl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridinyl, 5*H*-pyrrolo[2,3-*b*]pyrazinyl, 1*H*-pyrrolo[3,2-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, *1H*-indazolyl, wherein each R^5 is optionally substituted by one or more of the following: a) cyano, b) halo, c) a C_{1-4} alkyl group optionally substituted by one or more fluoro, d) a C_{1-4} alkoxy group optionally substituted by one or more fluoro, e) a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, f) or by a group $(CH_2)_zR^z$ in which z and w is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally

substituted by one or more of the following:cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, or a C_{1-4}alkoxy group optionally substituted by one or more fluoro;

as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, thereof.

The invention relates to a compound of the general formula (I)



I

wherein

R^1 represents cyano or a C_{1-4} alkoxy group optionally substituted by one or more fluoro, a C_{1-4} alkyl group optionally substituted by one or more fluoro, halo, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O atom, a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring,

n represents 0, 1, 2 or 3 ;

R^2 represents H or cyano or a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4} alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O, a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

R^3 represents H or a C_{1-4} alkyl group;

L^1 represents a $(CH_2)_pC_{3-10}$ cycloalkyl group in which p is 0 or1 and in which the cycloalkyl group may be monocyclic or bicyclic and optionally may be bridged provided that the two nitrogens bearing R^3 and R^4, respectively, are not linked to the same carbon

atom, and wherein one of the carbons may be replaced by O or the group -N(R^3) -L^1-, or the group L^1-N(R^4), together represent a saturated heterocyclic ring containing from 2 to 9 carbon atoms and the nitrogen bearing R^3 or R^4, respectively, which may be monocyclic or bicyclic with the proviso that L^1 does not represent 1,3-cyclopentyl or 1,4-cyclohexyl;

R^4 represents H or a C_{1-4} alkyl group optionally substituted by one or more of the following: fluoro or C_{1-4} alkoxy optionally substituted by one or more fluoro;

L^2 represents an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: fluoro or C_{1-4} alkyl;

L^2 may also represent a 5-6 membered carbocyclic 5-6 membered ring fused to R^5;

R^5 represents aryl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole each of which is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, or a group $(CH_2)_zR^z$ in which z is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally substituted by one or more cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4}alkoxy group optionally substituted by one or more fluoro as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, thereof.

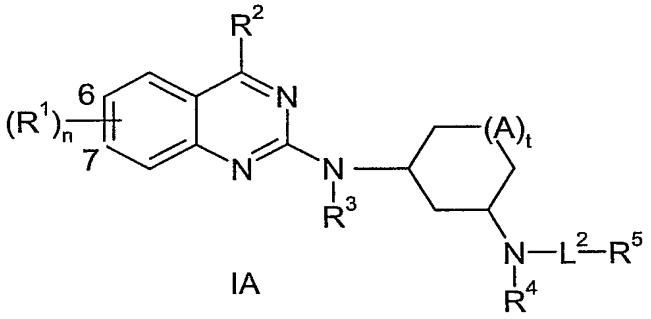
In a particular group of compound sof formula I, L^1 represents a $(CH_2)_pC_{3-10}$ cycloalkyl group in which p is 0 or 1 and in which the cycloalkyl group may be monocyclic or bicyclic and optionally may be bridged provided that the two nitrogens bearing R^3 and R^4, respectively, are not linked to the same carbon atom,and wherein one of the carbons may be replaced by O or the group -N(R^3) -L^1-, or the group L^1-N(R^4), together represent a saturated heterocyclic ring containing from 2 to 9 carbon atoms and the nitrogen bearing R^3 or R^4, respectively, which may be monocyclic or bicyclic.

In another aspect the invention provides compounds of formula I wherein
R^1 represents cyano or a C_{1-4} alkoxy group optionally substituted by one or more fluoro, a C_{1-4} alkyl group optionally substituted by one or more fluoro, halo, cyano, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O, a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring, n represents 0, 1, 2 or 3 ;
R^2 represents H or cyano or a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4} alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O, a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;
R^3 represents H or a C_{1-4} alkyl group;
L^1 represents a $(CH_2)_pC_{5-6}$ cycloalkyl group in which p is 0 or 1 and provided that there are 3 carbon atoms between the two nitrogens bearing R^3 and R^4, respectively, wherein one of the carbons of the cycloalkyl group may be replaced by O;
R^4 represents H or a C_{1-4} alkyl group optionally substituted by one or more of the following: fluoro or C_{1-4} alkoxy optionally substituted by fluoro;

L^2 represents an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: fluoro or C_{1-4} alkyl;
L^2 may also represent a 5-6 membered carbocyclic 5-6 membered ring fused to R^5;
R^5 represents aryl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole each of which is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a

C_{1-4} alkoxy group optionally substituted by one or more fluoro, or a group $(CH_2)_zR^z$ in which z is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally substituted by one or more cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4}alkoxy group optionally substituted by one or more fluoro or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, thereof.

A particular group of compounds of formula I is represented by formula IA



IA

in which

R^1 represents chloro, fluoro, methoxy or a group NR^aR^b in which R^a and R^b independently represent a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O;

n represents 0 or 1, and when n=1 the substituent is attached to either position 6 or 7

R^2 represents H or cyano or a C_{1-4}alkyl group, a C_{1-4}alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O, a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

R^3 represents H;

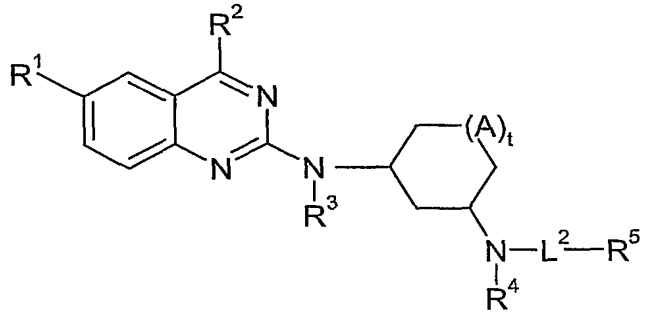
A represents CH_2 and t is 1;

R^4 represents H;

L^2 represents CH_2, $C(CH_3)_2$ or CF_2; and

R^5 represents aryl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole each of which is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, or a group $(CH_2)_zR^z$ in which z is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally substituted by one or more cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4}alkoxy group optionally substituted by one or more fluoro as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof.

Another particular group of compounds of formula I is represented by formula IB



IB

in which

R^1 represents H, cyano, methoxy, isopropoxy, dimethylamino, chloro or fluoro;

R^2 represents H, cyano, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4} alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O, R^3 represents H;

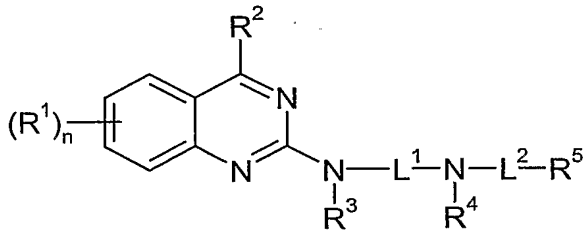
A represents CH_2 and t is 1;

R^4 represents H;

L^2 represents CH_2, $C(CH_3)_2$ or CF_2; and

R^5 represents aryl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole each of which is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, or a group $(CH_2)_zR^z$ in which z is 0 or 1 and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl, pyrazolyl, wherein each R^z is optionally substituted by one or more cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4}alkoxy group optionally substituted by one or more fluoro as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof.

Another particular group of compounds of formula I is represented by formula IC



IC

in which R^1 represents cyano or a C_{1-4} alkoxy group optionally substituted by one or more fluoro, a C_{1-4} alkyl group optionally substituted by one or more fluoro, halo, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O, a group $CONR^cR^d$ in which R^c and

R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring,

n represents 0, 1, 2 or 3 ;

R^2 represents H, cyano, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4} alkyl group or R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O, a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group or R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring;

R^3 represents H or a C_{1-4} alkyl group;

L^1 represents a $(CH_2)_pC_{7-10}$ cycloalkyl group in which p is 0 or 1 and in which the cycloalkyl group is fused bicyclic or bridged bicyclic provided that the two nitrogens bearing R^3 and R^4, respectively, are not linked to the same carbon atom, and wherein one of the carbons may be replaced by O;

R^4 represents H or a C_{1-4} alkyl group optionally substituted by one or more of the following: fluoro or C_{1-4} alkoxy, optionally substituted by one or more fluoro;

L^2 represents an alkylene chain $(CH_2)_s$ in which s represents 1, 2 or 3 wherein the alkylene chain is optionally substituted by one or more of the following: fluoro or C_{1-4} alkyl;

or L^2 may also represent a 5-6 membered carbocyclic ring fused to R^5;

R^5 represents aryl or a heterocyclic group selected from thienyl, furyl, pyridyl, pyrrolyl, quinolinyl, indolyl, benzofuranyl, benzo[*b*]thienyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyrazolyl, oxazolyl, imidazo[1,2-*a*]pyridine, 5*H*-pyrrolo[2,3-*b*]pyrazine, 1*H*-pyrrolo[3,2-*c*]pyridine, 1*H*-pyrrolo[2,3-*c*]pyridine, 1*H*-pyrrolo[2,3-*b*]pyridine, *1H*-indazole each of which is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, or by a group $S(O)_aR^y$ in which a is 0, 1 or 2 and R^y is phenyl optionally substituted by cyano, halo, a C_{1-4}alkyl group optionally substituted by one or more fluoro or a C_{1-4}alkoxy group optionally substituted by one or more fluoro, or a group $(CH_2)_zR^z$ in which z is 0 or and R^z represents phenyl or a heterocyclic group selected from thienyl, pyridyl, thiazolyl,

pyrazolyl, wherein each R^z is optionally substituted by one or more cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a C_{1-4}alkoxy group optionally substituted by one or more fluoro as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof..

Particularly R^1 represents H, cyano, fluoro, methoxy, isopropoxy, chloro or dimethylamino.

Particularly R^2 represents H, methyl, methoxy, isopropoxy, difluoromethoxy, trifluormethoxy, trifluoromethyl, dimethylamino, 1-pyrrolidinyl or 1-morpholinyl.

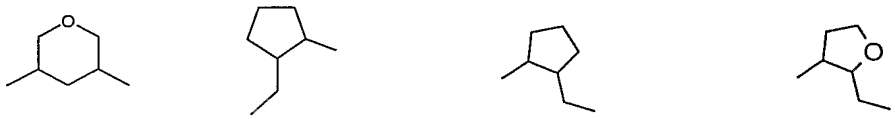
Particularly R^5 represents one or more of the following: 3-thienyl, 1-methylpyrrol-2-yl, 1-methylindol-3-yl, 2,4-dimethoxypyrimidin-5-yl, 2-(phenylsulfonyl)-1,3-thiazol-5-yl, 1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl, 1-[(2-chloro-1,3-thiazol-5-yl)methyl]-1*H*-indol-3-yl}, 5-(2-thienyl)thien-2-yl, 5-pyridin-2-yl-2-thienyl, 1,2,3-thiadiazol-4-yl, 4-chloro-1-methyl-1*H*-pyrazol-3-yl and quinolin-2-yl. Particularly R^5 represents one or more of the following : 3,4-dichlorophenyl, 6-(trifluoromethyl)pyridin-3-yl, and 2-(trifluoromethoxy)phenyl.

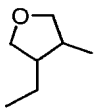
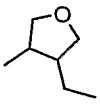
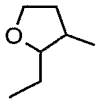
In one particular group of compounds of formula I B , R^1 represents H, fluoro, chloro or dimethylamino; R^2 represents H, methyl, methoxy, isopropoxy, difluoromethoxy, trifluormethoxy, trifluoromethyl, dimethylamino, 1-pyrrolidinyl or 1-morpholinyl, L^2 represents CH_2, A is CH_2 , t is 1; R^3 and $R^4$are each H, and R^5 represents one of the following : 3-thienyl, 1-methylpyrrol-2-yl, 1-methylindol-3-yl, 2,4-dimethoxypyrimidin-5-yl, 2-(phenylsulfonyl)-1,3-thiazol-5-yl, 1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl, 1-[(2-chloro-1,3-thiazol-5-yl)methyl]-1*H*-indol-3-yl}, 5-(2-thienyl)thien-2-yl, 5-pyridin-2-yl-2-thienyl, 1,2,3-thiadiazol-4-yl, 4-chloro-1-methyl-1*H*-pyrazol-3-yl and quinolin-2-yl.

Particularly in compounds of formula I, p is 0 L^1 is 1,3-cyclohexyl.

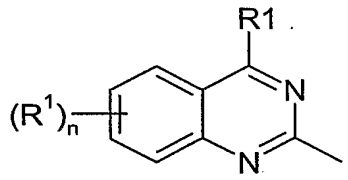
More particularly in compounds of formula I, IA, IB and IC the stereochemistry of the cycloalkyl carbon atoms to which the nitrogen atoms are attached is S, S.

Particularly in compounds of formula I, L^1 is selected from:



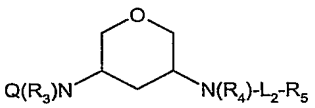




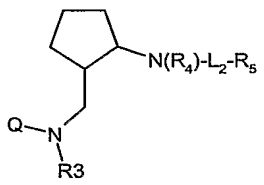
It will be understood that in the above the free bond to the left of the page is attached to the nitrogen bearing R^3 and the free bond to the right of the page is attached to the nitrogen bearing R^4. For the avoidance of doubt when Q represents

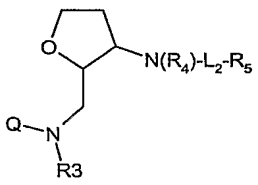


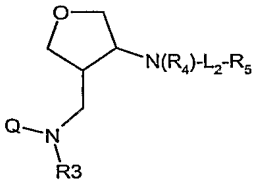
Q

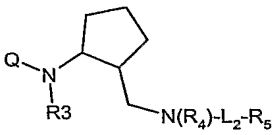
particular compounds of the invention are

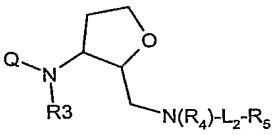


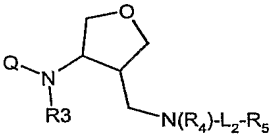












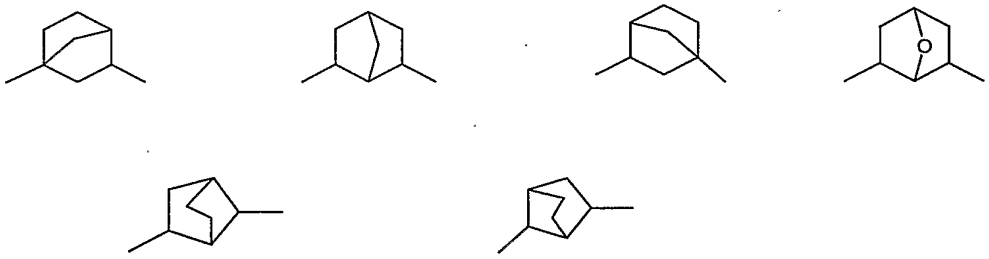
in which Q, R^3, R^4, L^2 and R^5 are as previously defined.

In a particular group of compounds of formula I, L^1 represents

a $(CH_2)_pC_{7-10}$ cycloalkyl group in which p is 0 or 1-and in which the cycloalkyl group is fused or bicyclic and optionally may be bridged provided that the two nitrogens bearing R^3 and R^4, respectively, are not linked to the same carbon atom, and wherein one of the carbons may be replaced by O or, alternatively, the group $-N(R^3)-L^1-$ or the group $L^1-N(R^4)$ together represent a saturated bicyclic heterocyclic ring containing from 2 to 9 carbon atoms and the nitrogen bearing R^3 or R^4 respectively.

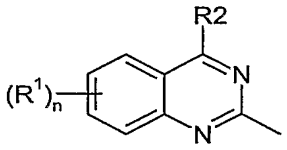
Alternatively, $N(R^3)-L^1-N(R^4)$ are joined together in a bicylic ring containing 6 to 8 carbon atoms and R^1, R^2, R^3, R^4, R^5, L^2, m and n are as defined above.

Examples where L^1 is bicyclic include



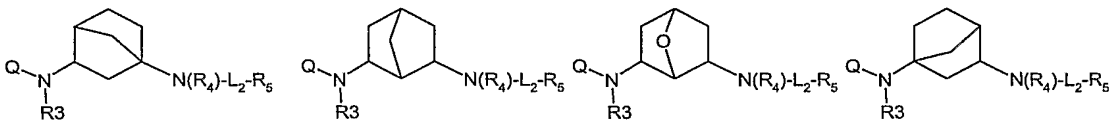
It will be understood that in the above the free bond to the left of the page is attached to the nitrogen bearing R^3 (or to the quinoline ring) and the free bond to the right of the page is attached to the nitrogen bearing R^4 (or to L2 or to R5).

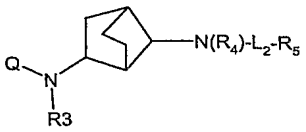
For the avoidance of doubt when Q represents



Q

examples of compounds where L^1 is bicyclic include





in which Q, R^3, R^4, L^2 and R^5 are as previously defined.

The term "pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula **I** is, for example, an acid-addition salt of a compound of Formula **I** which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium, calcium or magnesium salt, or an ammonium salt,or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl . Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halo" shall mean fluorine, chlorine, bromine or iodine.

Aryl means phenyl or naphthyl in definitions of R^5 each of which is optionally substituted as described above.

Examples of a C_{1-4} alkoxy group optionally substituted by one or more fluoro, include trifluoromethoxy, difluoromethoxy, fluoromethoxy and 4,4,4 –trifluorobutoxy.

Examples of a C_{1-4} alkyl group optionally substituted by one or more fluoro include trifluoromethyl, difluoromethyl and fluoromethyl.

Examples of a group OSO_2C_{1-4}alkyl, wherein the alkyl group is optionally substituted with one or more fluorine atoms include methylsulfonyloxy, ethylsulfonyloxy, n-propylsulfonyloxy, n-butylsulfonyloxy, 4,4,4-trifluorobutyl-1-sulfonyloxy and 3,3,3-trifluoropropyl-1-sulfonyloxy.

Examples of a group NR^aR^b in which R^a and R^b independently represent H or a C_{1-4}alkyl group include methylamino, ethylamino, propylamino, isopropylamino, butylamino dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino.

Examples of a group NR^aR^b in which R^a and R^b together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring optionally including an O include pyrrolidino, morpholino and piperidino.

Examples of a group $CONR^cR^d$ in which R^c and R^d independently represent H or a C_{1-4}alkyl group include N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl

Examples of a group $CONR^cR^d$ in which R^c and R^d together with the nitrogen atom to which they are attached represent a saturated 3 to 7 membered heterocyclic ring include pyrrolidinocarbonyl and piperidinocarbonyl.

Specific compounds of the invention are

N-(4-methylquinazolin-2-yl)-*N'*-(3-thienylmethyl)-*trans*- cyclohexane-1,3-diamine;

N^4,N^4-dimethyl-N^2-{-3-[(3-thienylmethyl)amino]-*trans*-cyclohexyl}quinazoline-2,4-diamine;

N^2-{-3-[(1-benzothien-3-ylmethyl)amino]-*trans*-cyclohexyl}-N^4,N^4-dimethylquinazoline-2,4-diamine;

N^4,N^4-dimethyl-N^2-(-3-{[(1-methyl-1*H*-indol-3-yl)methyl]amino}-*trans*-cyclohexyl)quinazoline-2,4-diamine;

N^4, N^4-dimethyl-*N*-2-((1S,3S)-3-{[2-(trifluoromethoxy)benzyl]amino}cyclohexyl)-quinazoline-2,4-diamine;

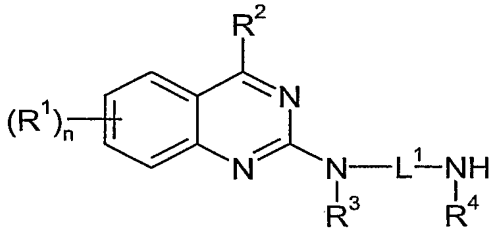
N^4, N^4-dimethyl-*N*-2-[(1S,3S)-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}amino)-cyclohexyl]quinazoline-2,4-diamine; and

N^{2-}{(1S,3S)-3-[(3,4-dichlorobenzyl)amino]cyclohexyl}-N^4-N^4-dimethylquinazoline-2,4-diamine;
and pharmaceutically acceptable salts thereof.

Methods of preparation

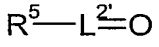
The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula I may be prepared by reacting a compound of formula II



II

in which R^1, R^2, R^3, R^4, L^1, and n are as previously defined with an aldehyde or a ketone of formula III

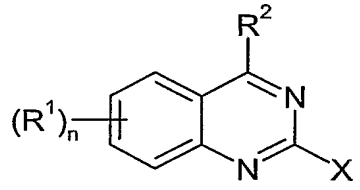


III

in which R^5 is as previously defined and $L^{2'}$ represents a group which after reaction of compounds II and III gives L^2 on reduction, under reductive alkylation conditions. For example, a compound of formula II and a compound of formula III may be reacted together at a temperature in the range of 0°C to 250°C, preferably in the range of 50°C to

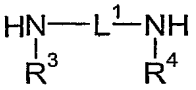
150°C, optionally in the presence of an inert solvent, for example methanol, dichloromethane or acetic acid in the presence of a reducing agent, for example sodium cyanoborohydride or optionally polymer supported cyanoborohydride.

Compounds of formula II may be prepared by reacting a compound of formula IV



IV

in which R^1, R^2, and n are as previously defined and X is halo, particularly chloro or bromo, with a compound of formula V



V

at a temperature in the range of 0°C to 250°C, preferably in the range of 50°C to 150°C in pyridine or optionally in the presence of an inert solvent, for example toluene or dioxane in the presence of a catalytic cross-coupling system for example $Pd(OAc)_2$ and 2-(di-^{t}butylphosphino)biphenyl or BINAP, and optionally in the presence of a base for example NaO^tBu or Cs_2CO_3.

Certain compounds of formula II and V are novel and are claimed as a further aspect of the present invention as useful intermediates.

Optionally one or both nitrogens in formula V may be protected prior to reaction with a compound of formula IV and then the compound of formula II obtained is deprotected prior to reaction with a compound of formula III. Amine protecting groups are known to those skilled in the art for example the t-Boc, Cbz or phtalimido groups.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. chemical

transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutically acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight. Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

The compounds of the invention may also be combined with other therapeutic agents which are useful in the treatment of disorders associated with obesity, psychiatric disorders, neurological disorders and pain.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Raynaud's syndrome , Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are

also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, and diseases related to the respiratory and gastrointestinal systems. The compounds are also potentially useful as agents for ceasing consumption of tobacco, treating nicotine dependence and/or treating nicotine withdrawal symptoms, reducing the craving for nicotine and as anti-smoking agents. The compounds may also eliminate the increase in weight that normally accompanies the cessation of smoking. The compounds are also potentially useful as agents for treating or preventing diarrhoea.The compounds are also potentially useful as agents for reducing the craving/relapse for addictive substances that include, but are not limited to psychomotor-active agents such as nicotine, alcohol, cocaine, amphetamines, opiates, benzodiazepines and barbiturates. The compounds are also potentially useful as agents for treating drug addiction and/or drug abuse.

The compounds of the present invention may also be used to prevent or reverse medication-induced weight gain, e.g. weight gain caused by antipsychotic (neuroleptic) treatment(s). The compounds of the present invention may also be used to prevent or reverse weight gain associated with smoking cessation.

Accordingly, it is desirable to provide a compound and method of treatment which will be active in reducing craving for the abused substance, and which does not exacerbate the sympathetic response rate caused by the abused substance and which has favorable pharmacodynamic effects.

The compounds are also potentially useful as agents for treating pain disorders , including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine.

In another aspect the present invention provides a compound of formula I as claimed in any previous claim for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders , including but not limited to acute and chronic nociceptive, inflammatory and

neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders, including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity.

In another aspect the present invention provides a method of treating obesity, type II diabetes, Metabolic syndrome and a method of preventing type II diabetes comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. For example, a compound of the present invention may be used in combination with a compound that affects thermogenesis, lipolysis, fat absortion, satiety, or gut motility. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors).

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding resin.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist ;

another Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

an SSRI;

a serotonin antagonist;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in

this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or

a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Working examples

The invention will now be described in more detail with the following examples that are not to be construed as limiting the invention.

Abbreviations

aq.	aqueous
Ac	acetyl
BINAP	*rac*-2,2'-Bis(diphenyl-phosphino)-1,1'-binaphtyl
Bu	butyl
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
ELS	evaporative light scattering
Et	ethyl
HEK	human embryotic kidney

HPLC	high performance liquid chromatography
LC	liquid chromatography
MS	mass spectroscopy
Pol-BH_3CN	(polystyrylmethyl)trimethylammonium cyanoborohydride (loading 4.1-4.3 mmol BH_3CN/g)
Pol-CHO	4-benzyloxybenzaldehyde polystyrene (loading ~2.66 mmol CHO/g)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Tris	trishydroxymethylaminomethane
t	tert
rt.	room temperature
sat.	saturated
br	broad
bs	broad singlet
bt	broad triplet
d	doublet
dd	doublet of doublets
m	multiplet
q	quartet
s	singlet
t	triplet
tt	triplet of triplets
td	triplet of doublets
bd	broad doublet

General Experimental Procedures

Flash column chromatography employed MERCK normal phase silica gel 60 Å (40-63 μm) or a Biotage Horizon Pioneer® HPFC system equipped with FLASH 12+M or FLASH 25+M or 40+M silica cartridges. Mass spectra were recorded on a Waters Micromass ZQ single quadrupole equipped with a pneumatically assisted electrospray interface (LC-MS). Purifications were performed on a Waters Prep LC 2000 with UV-

detection, equipped with a Kromasil 10 μm C8 250 mm x 20 mm column, or on a semi preparative HPLC, Shimadzu LC-8A, Shimadzu SPD-10A UV-vis.-detector equipped with a Waters Symmetry® 100 mm x 19 mm C18 5 μm column.

Automated HPLC purification was done using a Waters Fraction Lynx system equipped with UV, ELS and MS detection and an Ace C8 5μ 10 cm x 21,2 id column. The mobile phase was A: 95% CH_3CN and B: 5% CH_3CN + 95% 0,1 M NH_4OAc with a gradient from 100% B to 100% A in 10 minutes at 25 mL/min flow rate.

^1H NMR and ^{13}C NMR spectra were obtained at 298 K on a Varian Unity Plus 400 mHz, or a Varian Inova 500 MHz or a Varian Unity Plus 600 MHz or a Bruker Avance 300 MHz. Chemical shifts are given in ppm with the solvent residual peak as internal standard: $CDCl_3$ δ_H 7.26, δ_C 77.2; MeOH-d_4 δ_H 3.31, δ_C 49.0; DMSO-d_6 δ_H 2.50; δ_C 39.5 ppm. Microwave heating was performed using single node heating in a Smith Creator from Personal Chemistry, Uppsala, Sweden.

Analytical chiral HPLC was done using a Chiralcel OJ (250x4.6 mm i.d.) column with EtOH:Et_3N 100:0.1 as mobile phase at flow rate 1 mL/min and with UV detection at 254 or 350 nm.

Names/reference numbers of starting materials **(CAS no)**, etiher commercially available or prepared by published methods.

2-chloro-4-methylquinazoline, 6141-14-6; cyclohexane-1,3-diamine, 3385-21-5; 3-thiophenecarbaldehyde, 498-62-4; benzo[*b*]thiophene-3-carbaldehyde, 5381-20-4; 1-methylindole-3-carbaldehyde, 19012-03-4; *rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 98327-87-8; 2-trifluoromethoxybenzaldehyde, 94651-33-9; 6-(trifluoromethyl)nicotinaldehyde, 386704-12-7; 3,4-dichlorobenzaldehyde, 6287-38-3.

Preparation of Intermediates

Dibenzyl *trans*-cyclohexane-1,3-diylbiscarbamate

D-tartaric acid (15.77 g, 105 mmol) was added to a stirred solution of cyclohexane-1,3-diamine (12 g, 105 mmol, cis/trans ~2.6:1) in H_2O (80 mL). The resulting mixture was heated to ~60 °C and MeOH (800 mL) was slowly added. The mixture was allowed to attain rt and left for 3 days. The precipitate was filtered off and the filtrate was concentrated and redissolved in 1M NaOH (40 mL). To the stirred mixture at 0 °C was added benzyl chloroformate (9.56 g, 56 mmol) and 1M NaOH (40 mL). After 5 min, 1,4-dioxane (40 mL) was added and the mixture stirred for an additional 18 h at rt. The mixture

was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered and concentrated. Purification on a Biotage Horizon 40+M SiO_2 column gave 5.61 g (14%) of the title compound as a white solid.

^1H NMR (400 MHz, MeOH-d_4) δ 7.36-7.26 (m, 5H), 5.06 (bs, 2H), 3.77 (b, 2H), 1.73-1.42 (m, 8H).

LC-MS $[M+H]^+$ 383.4

(+) Dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate

The enantiomers of dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate were separated by preparative chiral chromatography. 7.27 g were dissolved in EtOH (56 mg/mL), repeated 2 mL (112 mg) injections on a Chiralcel OJ (250 x 20 mm i.d.), eluted with EtOH:Et_3N 100/0.1, 12 mL/min, gave 3.75 g of the title compound, 99.3% ee, $[\alpha]^{20}_D$ +2.7 (c 1.26, MeOH) and 2.45 g of (-)dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate, 83% ee.

(1*S*, 3*S*)-Cyclohexane-1,3-diamine dihydrochloride

(+)dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate (0.24 mmol, 0.090g) and 10% Pd on activated carbon (0.010 g) in EtOH (5mL) was stirred under a H_2-atmosphere. After 1 h, the mixture was filtered through Celite and concentrated to give 44 mg of the title compound (100%). The product was recrystallized from MeOH/Et_2O and the absolute configuration was determined by X-ray crystallography.

Examples

Example 1

***N*-(4-methylquinazolin-2-yl)-*N'*-(3-thienylmethyl)-*trans*- cyclohexane-1,3-diamine**

a) Dibenzyl *trans*-cyclohexane-1,3-diylbiscarbamate

D-tartaric acid (15.77 g, 105 mmol) was added to a stirred solution of cyclohexane-1,3-diamine (12 g, 105 mmol, cis/trans ~2.6:1) in H_2O (80 mL). The resulting mixture was heated to ~60 °C and MeOH (800 mL) was slowly added. The mixture was allowed to attain rt and left for 3 days. The precipitate was filtered off and the filtrate was concentrated and redissolved in 1M NaOH (40 mL). To the stirred mixture at 0 °C was added benzyl chloroformate (9.56 g, 56 mmol) and 1M NaOH (40 mL). After 5 min, 1,4-dioxane (40 mL) was added and the mixture stirred for an additional 18 h at rt. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered and concentrated. Purification on a Biotage Horizon 40+M SiO_2 column gave 5.61 g (14%) of the title compound as a white solid.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.36-7.26 (m, 5H), 5.06 (bs, 2H), 3.77 (b, 2H), 1.73-1.42 (m, 8H).

LC-MS $[M+H]^+$ 383.4

b) Benzyl (3-{benzyloxycarbonyl-[4-methylquinazolin-2-yl]amino}-*trans*-cyclohexyl)carbamate

A mixture of 2-chloro-4-methylquinazoline (1.70 g, 9.57 mmol), dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate (4.0 g, 10.5 mmol), Cs_2CO_3 (6.96 g, 21.38 mmol), $Pd(OAc)_2$ (0.213 g, 0.95 mmol), and BINAP (0.592 g, 0.95 mmol) in toluene/THF (23 mL/10 mL) was stirred at 90 °C under an atmosphere of nitrogen until LC/MS indicated that starting material was consumed. The reaction mixture was cooled to room temperature, diluted with MeOH and filtered through celite. The filtrate was evaporated to dryness. The residue was purified on a SiO_2 column eluted with heptane:EtOAc (1:1) to give 0.840 g of the title compound as a mixture of the bis- and mono-Cbz-protected compound.

LC-MS $[M+H]^+$ 525 and 391

c) *N*-(4-methylquinazolin-2-yl)-*trans*-cyclohexane-1,3-diamine

Benzyl (3-{benzyloxycarbonyl-[4-methylquinazolin-2-yl]amino}-*trans*-cyclohexyl)carbamate (1.25 g, 2.38 mmol) was dissolved in MeOH (50 mL). Pd-C (10%, containing 57.7% H_2O) (250 mg) was added and mixture was stirred at room temperature under a hydrogen atmosphere until LC-MS indicated that starting material was consumed. The reaction mixture filtered through celite and evaporated to dryness. The residue was dissolved in MeCN and purified by HPLC (Eluent A: H_2O containing 0.1% TFA; Eluent B: MeCN; gradient from 5% to 85% of eluent B) to give 0.306 g (50%) of the title compound.

^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.81-7.84 (d, 1H), 7.54-7.65 (m, 2H), 7.16-7.21 (m, 1H), 5.23 (br d, 1H), 4.45 (br s, 1H), 3.11 (m, 1H), 2.74 (s, 3H), 1.60-2.04 (m, 8H), 1.25-1.33 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 169.4, 158.3, 152.1, 133.7, 126.3, 125.4, 122.2, 119.7, 46.3, 46.2, 40.4, 35.2, 30.9, 21.7, 20.0.

LC-MS $[M+H]^+$ 257

d) *N*-(4-methylquinazolin-2-yl)-*N'*-(3-thienylmethyl)-*trans*- cyclohexane-1,3-diamine

N-(4-methylquinazolin-2-yl)-*trans*-cyclohexane-1,3-diamine (51 mg, 0.2 mmol), thiophene-3-carboxaldehyde (22 mg, 0.2 mmol) and sodium triacetoxyborohydride (90 mg,

0.4 mmol) was added to CH_2Cl_2 (5 ml). The mixture was stirred at rt for 48 h. All starting material was then consumed according to LC-MS so the reaction was quenched with saturated NH_4Cl and the mixture washed with water. The organic phase was separated and the solvent evaporated. The residue was was purified on a pre-packed Si-column (Isolute, 5 g) eluted with CH_2Cl_2/MeOH 10:1 to give 20 mg (28 %) of the title product.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.97(d, 1H), 7.68 (t, 1H), 7.55 (d, 1H), 7.42-7.36 (m, 2H), 7.26 (t, 1H), 7.13 (d, 1H), 4.43 (m, 1H), 4.17 (d, 2H), 3.30-3.24 (m, 1H), 2.77 (s, 3H), 2.51-2.43 (m, 1H), 2.13-2.06 (m, 1H), 1.88-1.72 (m, 5H), 1.62-1.51 (m, 1H)

^{13}C NMR (101 MHz, MeOH-d_4) δ 170.2, 158.2, 151.6, 134.0, 133.3, 127.8, 126.8, 126.0, 125.6, 125.2, 122.6, 119.5, 52.6, 45.8, 42.9, 32.8, 29.6, 28.9, 20.5, 19.4

LC-MS $[M+H]^+$ 353.0

Example 2

***N*^{4},*N*^{4}-dimethyl-*N*^{2}-{-3-[(3-thienylmethyl)amino]-*trans*-cyclohexyl}quinazoline-2,4-diamine**

a) Benzyl (3-{benzyloxycarbonyl-[4-(dimethylamino)quinazolin-2-yl]amino}-*trans*-cyclohexyl)carbamate

A mixture of (2-chloro-quinazolin-4-yl)-dimethyl-amine (2.73 g, 13.12 mmol, preparation see WO03028641), dibenzyl-*trans*-cyclohexane-1,3-diylbiscarbamate (5.52 g, 14.43 mmol, preparation see Example 1a), Cs_2CO_3 (9.62 g, 30 mmol), $Pd(OAc)_2$ (0.295 g, 1.31 mmol), and BINAP (0.817 g, 1.31 mmol) in toluene:THF (25 mL:13 mL) was stirred at 90 °C under nitrogen until LC-MS indicated that starting material was consumed. The reaction mixture was cooled to room temperature, diluted with MeOH (200 mL) and filtered through celite. The filtrate was then evaporated to dryness. The residue was purified on a SiO_2 column eluted with Heptane:EtOAc (1:1) to give 2.61 g, 4.71 mmol (36% yield) of the title compound.

LC-MS $[M+H]^+$ 554

b) *N*^{2}-(3-amino-*trans*-cyclohexyl)-*N*^{4},*N*^{4}-dimethyl-quinazoline-2,4-diamine

Benzyl (3-{benzyloxycarbonyl-[4-(dimethylamino)quinazolin-2-yl]amino}-*trans*-cyclohexyl)carbamate (2.61 g, 4.71 mmol) was dissolved in MeOH (50 mL). Pd-C (10%, containing 57.7% H_2O) (500 mg) was added and the mixture was stirred at room temperature under a hydrogen atmosphere until LC-MS indicated that starting material was

consumed. The reaction mixture was filtered through Celite and evaporated to dryness to give 1.12 g (83%) of the title compound.

^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.78-7.80 (d, 1H), 7.43-7.51 (m, 2H), 6.70-7.05 (m, 1H), 4.32 (br, 1H), 3.28 (s, 6H), 3.11 (m, 1H), 1.90 (m, 1H), 1.51-1.71 (m, 7H), 1.23-1.25 (m, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7, 164.8, 156.9, 133.0, 126.4, 123.7, 120.7, 111.8, 46.7, 46.4, 42.2, 40.4, 35.2, 31.2, 20.1.

LC-MS $[M+H]^+$ 286

c) N^4,N^4-dimethyl-N^2-{-3-[(3-thienylmethyl)amino]-trans-cyclohexyl}quinazoline-2,4-diamine

A solution of N^2-(3-amino-*trans*-cyclohexyl)-N^4,N^4-dimethyl-quinazoline-2,4-diamine (0.200 g, 0.70 mmol) and thiophene-3-carbaldehyde (0.078 g, 0.70 mmol) in MeOH:DCM (1:2, containing 6% HOAc, 8 mL) was stirred at ambient temperature for 75 min, after which a solution of $NaBH_3CN$ (0.176 g, 2.8 mmol) in MeOH (5 mL) was added. The reaction mixture was stirred at room temperature over night after which an additional 0.5 eq. of thiophene-3-carbaldehyde was added. The temperature was raised to 50 °C and stirred at this temperature until TLC indicated that starting material was consumed. Methanol (10 mL) was added and the reaction mixture was concentrated. The residue was first purified on SiO_2 eluted with DCM:MeOH (10:1) containing 1% Et3N and then dissolved in MeCN and further purified by prep. HPLC (Eluent A: H_2O containing 0.1% TFA; Eluent B: MeCN; gradient from 10% to 90% of eluent B) to give 0.106 g (40%) of the title compound.

^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.81-7.84 (d, 1H), 7.47-7.51 (m, 2H), 7.25-7.28 (m, 1H), 7.05-7.13 (m, s, 3H), 4.43 (br, 1H), 3.85 (s, 2H), 3.29 (s, 6H), 2.93-2.97 (m, 1H), 1.27-1.99 (m, 9H).

LC-MS $[M+H]^+$ 382.

Example 3

N^2-{-3-[(1-benzothien-3-ylmethyl)amino]-*trans*-cyclohexyl}-N^4,N^4-dimethylquinazoline-2,4-diamine

A solution of N^2-(3-amino-*trans*-cyclohexyl)-N^4,N^4-dimethyl-quinazoline-2,4-diamine (0.237 g, 0.83 mmol, from Example 2b) and benzo[*b*]thiophene-3-carbaldehyde (0.135 g, 0.83 mmol) in MeOH:DCM (1:2, containing 1% HOAc, 20 mL) was stirred at ambient

temperature for 1.5 h, after which a solution of $NaBH_3CN$ (0.104 g, 1.66 mmol) in MeOH (4 mL) was added. The reaction mixture was stirred at room temperature until TLC indicated that starting material was consumed. Methanol (20 mL) was added and the reaction mixture was concentrated. The residue was purified on SiO_2 eluted with DCM:MeOH (98:2) containing 2% Et_3N and finally DCM:MeOH (9:1) containing 2% Et_3N to give 0.310 g (86%) of the title compound. This material was dissolved in MeCN and further purified by HPLC (Eluent A: H_2O containing 0.1% TFA; Eluent B: MeCN; gradient from 10% to 80% of eluent B) to give 0.200 g (56%) of the title compound.

^1H NMR (300.1 MHz, MeOD-d_4) δ 7.82 (d, 1H), 7.76 (m, 1H), 7.45 (t, 1H), 7.05-7.33 (m, 5H), 7.01 (t, 1H), 4.32 (br s, 1H), 3.96 (s, 2H), 3.18 (s, 6H), 2.90 (m, 1H), 1.3-2.1 (m, 8H).

^{13}C NMR (75.5 MHz, MeOD-d_4) δ 164.7, 158.0, 153,3, 140.7, 138.5, 134.6, 132.3, 128.7, 128.0, 126.6, 124.2, 123.9, 123.3, 122.5, 121.4, 120.0, 111.8, 51.9, 46.0, 43.8, 40.9, 36.6, 31.3, 31.2, 19.8.

LC-MS $[M+H]^+$ 432.2.

Example 4

N^4,N^4-dimethyl-N^2-(-3-{[(1-methyl-1*H*-indol-3-yl)methyl]amino}-*trans*-cyclohexyl)quinazoline-2,4-diamine

A solution of N^2-(3-amino-*trans*-cyclohexyl)-N^4,N^4-dimethyl-quinazoline-2,4-diamine (0.24 g, 0.84 mmol, from Example 2b), 1-methylindole-3-carbaldehyde (0.134 g, 0.84 mmol) and $NaBH(OAc)_3$ (0.267 g, 1.26 mmol) in 1,2-dichloroethane (3 mL) and THF (1 mL) was stirred under a nitrogen atmosphere at ambient temperature for one day. A saturated solution of $NaHCO_3$ (5 mL, aq.) was added and the mixture was extracted with DCM (2x 10 mL). The combined organic phases were concentrated and the residue was purified by prep. HPLC (Eluent A: H_2O containing 0.1% TFA; Eluent B: MeCN; gradient from 20% to 80% of eluent B) to give 32 mg (9%) of the title compound.

^1H NMR (300.1 MHz, MeOD-d_4) δ 8.09 (d, 1H), 7.60-7.71 (m, 2H), 7.48 (d, 1H), 7.25-7.31 (m, 3H), 7.10 (t, 1H), 6.99 (t, 1H), 4.36-4.46 (m, 3 H), 3.70 (s, 3H), 3.43 (s, 6H), 2.43 (br d 1H), 1.64-2.30 (m, 11H), 1.50-1.63 (m, 1H).

^{13}C NMR (75.5 MHz, MeOD-d_4) δ 164.4, 138.4, 135.1, 131.8, 128.6, 128.5, 123.5, 123.3, 121.0, 120.4, 119.2, 111.9, 110.7, 105.7, 53.4, 48.0, 47.6, 42.6, 40.5, 34.2, 33.0, 30.3, 30.2, 20.6. LC-MS $[M+H]^+$ 429

Example 5

N^4,N^4-dimethyl-N^2-((1S,3S)-3-{[2-(trifluoromethoxy)benzyl]amino}cyclohexyl)quinazoline-2,4-diamine

The title compound was prepared according to Example 6 from N^2-(3-amino-*trans*-cyclohexyl)-N^4,N^4-dimethyl-quinazoline-2,4-diamine (40 mg, 0.140 mmol, from Example 2b) and 2-trifluoromethoxybenzaldehyde (27 mg, 0.142 mmol), and sodium borohydride (26 mg, 0.69 mmol). Yield: 41 mg (64%) of the title compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.49 (m, 1H), 7.43 (d, 1H), 7.38-7.34 (m, 2H), 7.15-7.11 (m, 2H), 7.03 (m, 1H), 4.95 (bs, 1H), 4.43 (m, 1H), 3.83 (d, 1H), 3.81 (d, 1H), 3.26 (s, 6H), 2.93 (m, 1H), 190-1.70 (m, 5H), 1.65-1.55 (m, 2H), 1.41 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 157.9, 154.1, 147.9, 139.6, 132.0, 129.2, 129.0, 125.8, 125.2, 122.1, 120.7, 119.6, 118.7, 112.0, 52.1, 50.5, 45.9, 41.7, 37.7, 32.0, 31.9, 20.1. LC-MS $[M+H]^+$ 460.1.

Example 6

N^4,N^4-dimethyl-N^2-[(1S,3S)-3-({[6-(trifluoromethyl)pyridin-3-yl]methyl}amino)cyclohexyl]quinazoline-2,4-diamine

A solution of N^2-(3-amino-*trans*-cyclohexyl)-N^4,N^4-dimethyl-quinazoline-2,4-diamine (35 mg, 0.123 mmol, from Example 2b), 6-(trifluoromethyl)nicotinaldehyde (22 mg, 0.125 mmol) in 2 mL of methanol was allowed to react overnight. Sodium borohydride (23 mg, 0.61 mmol) was added and the mixture was stirred for 30 min before 1 mL of 2M HCl was added. After 5 min the mixture was made alkaline by addition of 2M NaOH and 20 mL of water. The mixture was extracted three times with EtOAc and the combined organic layer was washed with water, dried over Na_2SO_4 and evaporated. The crude material was chromatographed on a prepacked 5 g Isolute Silica gel column with DCM:MeOH:TEA 100:5:1. Yield: 41 mg (75%) of the title compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.87 (d, 1H), 7.80 (d, 1H), 7.58 (d, 1H), 7.47 (m, 1H), 7.42 (d, 1H), 7.02 (m, 1H), 5.07 (bs, 1H), 4.39 (m, 1H), 3.92 (d, 1H), 3.89 (d, 1H), 3.25 (s, 6H), 2.93 (m, 1H), 1.90-1.70 (m, 5H), 1.65-1.53 (m, 2H), 1.40 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 158.0, 153.9, 150.0, 147.4, 147.1, 146.7, 146.4, 140.1, 137.1, 132.4, 126.1, 126.0, 125.3, 123.2, 120.1, 120.3, 120.1, 117.8, 112.3, 52.6, 48.3, 46.1, 41.9, 37.7, 32.0, 20.2. LC-MS $[M+H]^+$ 445.1

Example 7

N^2-{(1S,3S)-3-[(3,4-dichlorobenzyl)amino]cyclohexyl}- N^4,N^4-dimethylquinazoline-2,4-diamine

The title compound was prepared according to Example 6 from N^2-(3-amino-*trans*-cyclohexyl)-N^4,N^4-dimethyl-quinazoline-2,4-diamine (35 mg, 0.123 mmol, from Example 2b), 3,4-dichlorobenzaldehyde (22 mg, 0.125 mmol) and sodium borohydride (23 mg, 0.61 mmol). Yield: 36 mg (66%) of the title compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (m, 1H), 7.51 (m, 1H), 7.48-7.44 (m, 2H), 7.34 (d, 1H), 7.17 (dd, 1H), 7.05 (m, 1H), 4.43 (m, 1H), 3.80 (d, 1H), 3.78 (d, 1H), 3.28 (s, 6H), 2.94 (m, 1H), 1.90-1.70 (m, 5H), 1.65-1.55 (m, 2H), 1.41 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 158.0, 147.0, 141.7, 132.4, 130.7, 130.4, 130.1, 127.6, 126.1, 125.2, 120.1, 52.4, 50.3, 46.4, 46.1, 41.2, 37.8, 32.0, 20.2, 11.7.

LC-MS $[M+H]^+$ 444.1/446.1/448.1.

Pharmacological Properties

MCH1 receptor radioligand binding.

Assays were performed on membranes prepared from CHO-K1 cells expressing the human Melanin concentrating hormone receptor 1 (MCH1r). Assays were performed in a 96-well plate format in a final reaction volume of 200µl per well. Each well contained 6 µg of membrane proteins diluted in binding buffer (50 mM Tris, 3 mM $MgCl_2$, 0.05 % bovine serum albumin (BSA) and the radioligand ^{125}I-MCH (IM344 Amersham) was added to give 10 000 cpm (counts per minute) per well. Each well contained 2µl of the appropriate concentration of competitive antagonist prepared in DMSO and left to stand at 30 °C for 60 minutes. Non-specific binding was determined as that remaining following incubation with 1µM MCH (Melanin concentrating hormone, H-1482 Bachem). The reaction was terminated by transfer of the reaction to GF/A filters using a Micro96 Harvester (Skatron Instruments, Norway). Filters were washed with assay buffer. Radioligand retained on the filters was quantified using a1450 Microbeta TRILUX (Wallac , Finland).

Non-specific binding was subtracted from all values determined. Maximum binding was that determined in the absence of any competitor following subtraction of the value determined for non-specific binding. Binding of compounds at various concentrations was plotted according to the equation

y = A+((B-A)/1+((C/x)^D)))

and IC_{50} estimated where

A is the bottom plateau of the curve i.e. the final minimum y value

B is the top of the plateau of the curve i.e. the final maximum y value

C is the x value at the middle of the curve. This represents the log EC50 value when A + B = 100

D is the slope factor.

x is the original known x values.

y is the original known y values.

The compounds exemplified herein had an IC_{50} of less than 2 μM in the abovementioned human MCHr binding assay. Preferred compounds had an activity of less than 1 μmolar. For example, the following IC_{50} was obtained for the compound of Example 4: 0.015 μM. Assays were also performed on membranes prepared from HEK293 cells stably expressing the rat Melanin concentrating hormone receptor 1 (MCH1r) (Lembo et al. Nature Cell Biol **1** 267-271). Assays were performed in a 96-well plate format in a final reaction volume of 200μl per well. Each well contained 5μg of membrane proteins diluted in binding buffer (50 mM Tris, 3 mM $MgCl_2$, 0.05 % bovine serum albumin (BSA) and the radioligand ^{125}I-MCH (IM344 Amersham) was added to give 10 000 cpm (counts per minute) per well. Each well contained 2μl of the appropriate concentration of competitive antagonist prepared in DMSO and left to stand at room temperature for 60 minutes. Non-specific binding was determined as that remaining following incubation with 1μM MCH (Melanin concentrating hormone, H-1482 Bachem). The reaction was terminated by transfer of the reaction to GF/A filters using a Micro96 Harvester (Skatron Instruments, Norway). Filters were washed with assay buffer. Radioligand retained on the filters was quantified using a1450 Microbeta TRILUX (Wallac , Finland).